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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,475	10/10/2001	Ryuichi Morishita	6235-59221	4309

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,475	MORISHITA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14,23-26,44-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14,23-26,44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 9, 11, 12, 14, 23-26, and 44-50 are pending.

Applicant's traversal, the cancellation of claims 16 and 27, the amendment of claims 9, 14, 23, 44, and 47 and the addition of claims 48-50 filed on 9/14/05 are acknowledged and considered by the examiner.

The indicated allowability of claims 16, 27, and 44-47 is withdrawn in view of the newly discovered reference(s) to Morishita et al. (EP 0847757). Rejections based on the newly cited reference(s) follow.

Election/Restrictions

The instant application contains species in claim 11, 24, and new claim 45 drawn to nonelected species with traverse in paper filed on 7/7/02.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/14/05 was filed after the mailing date of the non-final rejection on 6/17/05. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 11, 12, 14, 23, 24, 25, 26, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 98/19712, cited on a PTO-1449) taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local

News Section (Dec. 14, 1998) (cited on an PTO-1449), and Li et al. (US 6,066,123) in further view of Morishita et al. (EP 0847757).

Isner teaches a method of treating limb ischemia in a subject using a nucleic acid encoding an endothelial cell mitogen selected from growth factor proteins, including hepatocyte growth factor (HGF). See pages 16-17. However, Isner does not specifically teach using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease in a subject. In addition, Isner does not specifically teach administering the nucleic acid once every few weeks or every few days to the subject.

However, at the time the invention was made, the problems with blood circulation deficiency in lower limb diabetic ischemic disease was well known to one of ordinary skill in the art. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98. In addition, there was a reasonable expectation of success for gene therapy using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98.

In addition, at the time the invention was made, short-term expression of a nucleic acid *in vivo* because of the short half-life of HGF and/or nucleic acid, and/or inactivation of the nucleic acid, and/or natural maturation and sloughing off of the transformed cell was well known to one of ordinary skill in the art and several applications (e.g., every few days or every few weeks) of the nucleic acid would be required to treat the ischemic disease in the subject. See Li et al. (column 8).

In addition, at the time the invention was made, Morishita teaches that the content of HGF gene in a medicament may be appropriately varied depending upon disease being treated, target organs, patient's age or body weight, etc. (page 5). It is appropriate to administer a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when calculated as the HGF gene. The dose may be divided into several days or a few months (page 5). Administering a nucleic acid encoding HGF using a Sendai virus (HVJ)-liposome was well known to one of ordinary skill in the art as exemplified by Morishita et al. (page 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98, and Li et al. in further view of Morishita et al., namely to use a nucleic acid encoding HGF in a method of treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and use a nucleic acid encoding HGF in the method because of the problems with blood circulation is associated with lower limb diabetic ischemic disease and HGF is well known to one of ordinary skill in the art for treating problems with blood circulation.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98, and Li et al. in further view of Morishita et al., namely to administer a nucleic acid encoding HGF once every few days or every few weeks for treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings

and administer the nucleic acid encoding HGF once every few days or few weeks because of the problems associated with delivering nucleic acid in vivo.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner et al. taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998), Li et al. and Morishita et al., namely to use HVJ-liposome for delivering a nucleic acid encoding HGF in the method. One of ordinary skill in the art would have been motivated to combine the teachings, as a matter of designer's choice, and use HVJ-liposome for introducing the nucleic acid into the subject because HVJ-liposome is well known to one of ordinary skill in the art for improving DNA delivery of a liposome comprising DNA to a cell.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 and Li et al., in further view of Morishita et al., namely to administer a nucleic acid encoding HGF, wherein at least 50 μg of the HGF is administered to the subject. One of ordinary skill in the art would have been motivated to combine the teachings and administer at least 50 μg of the HGF because Morishita teaches that it is appropriate for one of ordinary skill in the art to administer HGF gene at a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when treating a disease.

MPEP 2144.05 recites: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is

evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

This is the case here. The specification does not disclose that the limitation in instant claims is critical for one of ordinary skill in the art to practice the claimed invention.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/14/05 have been fully considered but they are not persuasive.

In response to applicant's argument that claims 9 and 23 have been amended to include the phrase at "least 50 μg" in claims 16 and 27 was found to be free of the prior art, the argument is not found persuasive because upon further consideration (See MPEP 2144.05) and a further search of the prior art, the limitation was well known to one of ordinary skill in the art for using HGF gene as a medicament.

Claims 44-47 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 98/19712, cited on a PTO-1449) taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cited on an PTO-1449) in further view of Morishita et al. (EP 0847757).

Isner teaches a method of treating limb ischemia in a subject using a nucleic acid encoding an endothelial cell mitogen selected from growth factor proteins, including hepatocyte

growth factor (HGF). See pages 16-17. However, Isner does not specifically teach using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease in a subject.

However, at the time the invention was made, the problems with blood circulation deficiency in lower limb diabetic ischemic disease was well known to one of ordinary skill in the art. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98. In addition, there was a reasonable expectation of success for gene therapy using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98.

In addition, at the time the invention was made, Morishita teaches that the content of HGF gene in a medicament may be appropriately varied depending upon disease being treated, target organs, patient's age or body weight, etc. (page 5). It is appropriate to administer a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when calculated as the HGF gene. The dose may be divided into several days or a few months (page 5). Administering a nucleic acid encoding HGF using a Sendai virus (HVJ)-liposome was well known to one of ordinary skill in the art as exemplified by Morishita et al. (page 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Morishita et al., namely to use a nucleic acid encoding HGF in a method of treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and use a nucleic acid encoding HGF in the method because

of the problems with blood circulation is associated with lower limb diabetic ischemic disease and HGF is well known to one of ordinary skill in the art for treating problems with blood circulation.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner et al. taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998), and Morishita et al., namely to use HVJ-liposome for delivering a nucleic acid encoding HGF in the method. One of ordinary skill in the art would have been motivated to combine the teachings, as a matter of designer's choice, and use HVJ-liposome for introducing the nucleic acid into the subject because HVJ-liposome is well known to one of ordinary skill in the art for improving DNA delivery of a liposome comprising DNA to a cell.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Morishita et al., namely to administer a nucleic acid encoding HGF, wherein at least 50 μg of the HGF is administered to the subject. One of ordinary skill in the art would have been motivated to combine the teachings and administer at least 50 μg of the HGF because Morishita teaches that it is appropriate to administer a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when calculated as the HGF gene.

MPEP 2144.05 recites: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general

conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

This is the case here. The specification does not disclose that the limitation in instant claims is critical for one of ordinary skill in the art to practice the claimed invention.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/14/05 have been fully considered but they are not persuasive for the reasons set forth under the previous 103(a) rejection.

Response to Arguments

Applicant's arguments, see page 6, filed 9/14/05, with respect to 112 first paragraph have been fully considered and are persuasive. The rejection of claims 9, 11, 12, 14, 16, 23-27, 44-47 has been withdrawn.

Conclusion

See WO 97/14307 (pages 5 and 11) cited on a previous PTO-1449. The WO document supports that the limitation "at least 50 μg" was well known to one of ordinary skill in the art at the time the invention was made for using a nucleic acid encoding an angiogenic protein (HGF) at about 1 to 4000 μg to treat an ischemic tissue.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Brian Whiteman
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